Claims

1. Use of at least one inhibitor of at least one ABC-transporter capable of transporting hyaluronan across a lipid bilayer, for the preparation of a pharmaceutical composition for the treatment of a disease which is associated with an excess transport of hyaluronan across a lipid bilayer.

2. The use of claim 1, wherein said inhibitor(s) specifically reduce(s) the transport of hyaluronan across a lipid bilayer mediated by at least one of said ABC-transporter(s).

3. The use of claims 1 or 2, wherein said ABC-transporter(s) is(are) a mammalian ABC-transporter(s).

4. The use of any one of claims 1 to 3, wherein said ABC-transporter(s) is(are) a human ABC-transporter(s).

5. The use of any one of claims 1 to 4, wherein said human ABC-transporter(s) is(are) a member of the human ABCB (MDR)-subfamily, the ABCA subfamily and/or the human ABC-C (MRP)-subfamily.

6. The use of any one of claims 1 to 5, wherein said ABC-transporter(s) is(are) comprised in a chondrocyte cell, preferably a human chondrocyte cell.

7. The use of any one of claims 1 to 6, wherein said inhibitor(s) is(are) selected from the group consisting of:

   (a) an inhibitor of a member of the ABCB (MDR)-subfamily selected from Verapamil, Valspodar (PSC833), Elacridar (GF-120918), Bericodar (VX-710), Tariquidar (XR-9576), XR-9051, S-9788, LY-335979, MS 209, R101933; OC-144-093; Quinidine, Chloripramine, Nicardipine,

Nifedipine, Amlodipine, Felodipine, Manidipine, Flunarizine, Nimodipine, Pimozide, Lomerizine, Bepridil, Amiloride, Almitrine, Amiodarone, Imipramine, Clomiphene, Tamoxifen, Toremifene, Ketocanazole, Terfenadine, Chloroquine, Mepacrin, Diltiazem, Niguldipine, Prenylamine, Gallopamil, Tiapamil, Dex-Verapamil, Dipyridamole, Pimozide, Haloperidol, Chlorpromazine, Trifluoperazine, Fluphenazine, Reserpin, Clopenthixol, Flupentixol, N-acetyldaunorubicin, Vindoline, N2762-14, N276-14, N276-17, B9309-068, BIBW-22, Carvedilol, Clofazimine, Ketoconazole, Lovastatin, N-Norgallopamil, Simvastatin, Troleandomycin, Vinblastin, Itraconazole, Econazole, Oligomycine, Cyclosporin and Rapamycin; and/or

(b) an inhibitor of a member of the ABCA subfamily selected from Glyburide, DIDS (4,4-diisothiocyanatostilbene-2,2-disulfonic acid), Bumetanide, Furosemide, Sulfobromophthalein, Diphenylamine-2-carboxylic acid and Flufenamic acid; and/or

(c) an inhibitor of a member of the human ABC-C (MRP)-subfamily selected from MK-571, Benzbromaron, PAK-104P, Probenecid, Sulfinpyrazone, Indomethacin, Merthiolate and Ethacrynic acid; and/or

(d) (an) antibody(ies) or functional fragments thereof which is(are) specifically recognizing one or more ABC-transporter(s) capable of transporting hyaluronan across a lipid bilayer; and/or

(e) (an) antisense oligomere(s), iRNA and/or siRNA directed against one or more ABC-transporter(s) capable of transporting hyaluronan across a lipid bilayer; and/or

(f) (an) aptamer(s) directed against one or more ABC-transporter(s) capable of transporting hyaluronan across a lipid bilayer.

8. The use of any one of claims 1 to 7, wherein said disease which is associated with an excess transport of hyaluronan across a lipid bilayer is arthritis.

9. The use of claim 8, wherein said arthritis is characterized by a degeneration and/or a destruction of cartilage.

10. The use of any one of claims 8 or 9, wherein said arthritis is osteoarthritis, (juvenile) chronic arthritis, rheumatoid arthritis, psoriatic arthritis, *A. mutilans*, septic arthritis, infectious arthritis and/or reactive arthritis.

11. The use of any one of claims 1 to 10, wherein said inhibitor(s) is(are) to be administered prophylactically.

12. The use of any one of claims 1 to 10, wherein said inhibitor(s) is(are) to be administered therapeutically.

13. A method of screening for a compound which is suitable for the treatment of a disease which is associated with an excess transport of hyaluronan across a lipid bilayersaid method comprising:

(a) contacting an isolated lipid bilayer comprising at least one ABC-transporter which is capable of transporting hyaluronan with a test compound and an indicator compound;

(b) measuring the effect of the test compound on the transport of the indicator compound across the lipid bilayer; and

(c) identifying test compounds which reduce the transport of the indicator compound.

14. A method of screening for a compound which reduces the transport of hyaluronan mediated by (an) ABC-transporter(s), said method comprising:

(a) contacting an isolated lipid bilayer comprising at least one ABC-transporter which is capable of transporting hyaluronan with a test compound and an indicator compound;

(b) measuring the effect of the test compound on the transport of the indicator compound across the lipid bilayer; and

(c) identifying test compounds which reduce the transport of the indicator compound.

15. A method of screening for a compound which is suitable for the treatment of a disease which is associated with an excess transport of hyaluronan across a lipid bilayer said method comprising:
    (a) contacting a cell comprising at least one ABC-transporter which is capable of transporting hyaluronan with a test compound and an indicator compound;
    (b) measuring the effect of the test compound on the transport of the indicator compound across a lipid bilayer of the cell; and
    (c) identifying compounds which reduce the transport of the indicator compound.

16. A method of screening for a compound which reduces the transport of hyaluronan mediated by (an) ABC-transporter(s), said method comprising:
    (a) contacting a cell comprising at least one ABC-transporter which is capable of transporting hyaluronan with a test compound and an indicator compound;
    (b) measuring the effect of the test compound on the transport of the indicator compound across a lipid bilayer of the cell; and
    (c) identifying compounds which reduce the transport of the indicator compound.

17. The method of any one claim 13 to 16 of screening for a compound which specifically reduces the transport of hyaluronan mediated by said ABC-transporter.

18. The method of any one of claims 15 to 17, wherein the cell is a bacterial, an insect, a fungal or an animal cell.

19. The method of claim 18, wherein said animal cell is a mammalian cell or a mammalian cell line.

20. The method of claim 19, wherein said mammalian cell or mammalian cell line is derived from human, horse, swine, goat, cattle, mouse or rat.

21. The method of claim 19 or 20, wherein the cell or cell line is a chondrocyte, a fibroblast, a synovial cell, an endothelial cell, a macrophage, a tumour cell, a smooth muscle cell, a melanoma cell or a mesothelioma cell.

22. The method of claim 21, wherein said cell is comprised in a tissue.

23. The method of claim 22, wherein said tissue is cartilage tissue.

24. The method of any one of claims 19 to 23, wherein said cell or said tissue is derived from a mammalian subject preferably a human subject which suffers from a disease which is associated with an excess transport of hyaluronan across a lipid bilayer, e.g. arthritis.

25. The method of any one of claims 19 to 23, wherein the cell comprises at least one heterologous ABC-transporter.

26. The method of any one of claims 19 to 25, wherein said cell and/or said tissue is comprised in a non-human animal.

27. The method of any one of claims 15 to 25 which is *ex vivo*.

28. A method of screening for a compound which is suitable for the treatment of a disease which is associated with an excess transport of hyaluronan across a lipid bilayer said method comprising:

(a) contacting a cell derived from said subject which comprises at least one ABC-transporter with a test compound to be tested;

(b) measuring the effect of the test compound on the transport of an indicator compound across a lipid bilayer of said cell; and

(c) identifying compounds which reduce the transport of hyaluronan across the lipid bilayer of said cell.

29. The method of claim 28, wherein said cell is comprised in a tissue.

30. The method of any one of claims 28 to 29, wherein said cell is a chondrocyte.

31. The method of any one of claims 28 to 30, wherein said subject is a mammalian subject.

32. The method of claim 31, wherein said mammalian subject is a human, a horse, a camel, a dog, a cat, a pig, a cow or a goat.

33. The method of any one of claims 28 to 32, wherein said cell is contacted with a compound selected from the group consisting of:

(a) an inhibitor of a member of the ABCB (MDR)-subfamily selected from Verapamil, Valspodar (PSC833), Elacridar (GF-120918), Bericodar (VX-710), Tariquidar (XR-9576), XR-9051, S-9788, LY-335979, MS 209, R101933; OC-144-093; Quinidine, Chloripramine, Nicardipine, Nifedipine, Amlodipine, Felodipine, Manidipine, Flunarizine, Nimodipine, Pimozide, Lomerizine, Bepridil, Amiloride, Almitrine, Amiodarone, Imipramine, Clomiphene, Tamoxifen, Toremifene, Ketocanazole, Terfenadine, Chloroquine, Mepacrin, Diltiazem, Niguldipine, Prenylamine, Gallopamil, Tiapamil, Dex-Verapamil, Dipyridamole, Pimozide, Haloperidol, Chlorpromazine, Trifluoperazine, Fluphenazine, Reserpin, Clopenthixol, Flupentixol, N-acetyldaunorubicin, Vindoline, N2762-14, N276-14, N276-17, B9309-068, BIBW-22, Carvedilol, Clofazimine, Ketoconazole, Lovastatin, N-Norgallopamil, Simvastatin, Troleandomycin, Vinblastin, Itraconazole, Econazole, Oligomycine, Cyclosporin and Rapamycin; and/or

(b) an inhibitor of a member of the ABCA subfamily selected from Glyburide, DIDS (4,4-diisothiocyanatostilbene-2,2-disulfonic acid), Bumetanide, Furosemide, Sulfobromophthalein, Diphenylamine-2-carboxylic acid and Flufenamic acid; and/or

(c) an inhibitor of a member of the human ABC-C (MRP)-subfamily selected from MK-571, Benzbromaron, PAK-104P, Probenecid, Sulfinpyrazone, Indomethacin, Merthiolate and Ethacrynic acid; and/or

(d) (an) antibody(ies) or functional fragments thereof which is(are) specifically recognizing one or more ABC-transporter(s) capable of transporting hyaluronan across a lipid bilayer; and/or

(e) (an) antisense oligomere(s), iRNA and/or siRNA directed against one or more ABC-transporter(s) capable of transporting hyaluronan across a lipid bilayer; and/or

(f) (an) aptamer(s) directed against one or more ABC-transporter(s) capable of transporting hyaluronan across a lipid bilayer.

34. The method of any one of claims 13 to 33 further comprising a step of refining the compound identified, said method comprising the steps of:

(a) identification of the binding sites of the compound and the ABC-transporter(s);

(b) molecular modelling of the binding site of the compound; and

(c) modification of the compound to improve its binding specificity for the ABC-transporter(s).

35. The method of any one of claims 13 to 34, further comprising the step of formulating the compound identified, refined or modified with a pharmaceutically active carrier and/or diluent.

36. A method for manufacturing a pharmaceutical composition comprising the steps of any one of claims 13 to 35 and the step of formulating the compound screened in a pharmaceutically acceptable form.

37. A method of preventing, ameliorating and/or treating the symptoms of a disease which is associated with an excess transport of hyaluronan across a lipid bilayer, e.g. arthritis in a subject comprising administering at least one inhibitor of at least one ABC-transporter capable of transporting hyaluronan across a lipid bilayer to the subject, preferably an mammalian subject, such that the a disease which is associated with an excess transport of hyaluronan across a lipid bilayer, e.g. arthritis is prevented, ameliorated and/or treated.

38. The method of claim 37, wherein said arthritis is characterized by a degeneration and/or a destruction of cartilage.

39. The method of claim 37 or 38, wherein said arthritis is osteoarthritis, (juvenile) chronic arthritis, rheumatoid arthritis, psoriatic arthritis, *A. mutilans*, septic arthritis, infectious arthritis and/or reactive arthritis.

40. The method of claim 39 wherein said arthritis is osteoarthritis.

41. The method of any one of claims 37 to 39, wherein said mammalian subject is a human, a horse, a camel, a dog, a cat, a pig, a cow or a goat.

42. The use of any one of claims 1 to 12 or the method of any one of claims 13 to 41, wherein said ABC-transporter is MRP5 (ABCC5), ABCC11 and/or ABCC12.

43. Use of an inhibitor of at least one ABC-transporter capable of transporting hyaluronan across a lipid-bilayer, wherein said at least one ABC-transporter is MRP5 (ABCC5), ABCC11 and/or ABCC12, for the preparation of a pharmaceutical composition for the treatment of osteoarthritis.

44. The use of claim 43, wherein said at least one ABC-transporter is MRP5 (ABCC5).

45. Use of Zaprinast® for the preparation of a pharmaceutical composition for the treatment of arthritis, preferably rheumatoid arthritis or osteoarthritis.

46. Use of Elacridar (GF-120918), Valspodar (PSC-833), Bericodar (VX-710), Tariquidar (XR-9576), S-9788, Ly-335979, OC-144-093 and/or Lysodren® for the preparation of a pharmaceutical composition for the treatment of osteoarthritis.